

**Please amend the specification as follows:**

Note: All amendments are in reference to the paragraph numbers of the published application (Publication Number 2003/0143746).

**Please amend paragraph 0021 as follows:**

It is a yet another object of the invention to provide a body analyte monitoring system that minimizes the size of the system so that it may be comfortably worn, for example and not by limitation, by providing the system with a skin adhesive for adhering the system to the body, or further by example by providing a strap to hold the system in place against the body. Accordingly, in a preferred embodiment of the invention, the fluid driving means for the perfusate, reagent, and calibration fluids is a pressurized fluid reservoir system. This eliminates the need for rotating electrical machinery such as a pump and simultaneously reduces the size of the battery since power to drive the pump isn't needed.

**Please add the following paragraphs immediately following paragraph 0027:**

Fig. 5. shows a representation of the self-calibrating body analyte monitor in contact with skin worn on a body part.

Fig. 6 shows a representation of the self-calibrating body analyte monitor being held on the skin by an adhesive and being used in conjunction with an insulin delivery system.

**Please amend paragraph 0028 as follows:**

A schematic of an apparatus for obtaining periodic, self-calibrated measurements of a body analyte is shown in Figure 1. The apparatus is comprised of microfluidics chip 1 which is attached, either integrally or by a fluid connecting means, to microdialysis needle 3.

Microfluidics chip 1, shown in greater detail in Figure 2, is supplied with perfusate through fluid supply line 31 from perfusate reservoir 20, with enzyme solution through fluid supply line 32 from enzyme solution reservoir 21, and with calibration fluid through fluid supply line 33 from calibration fluid reservoir 22. The perfusate is preferably an isotonic solution composed of saline and containing other compounds to make the fluid biocompatible. The enzyme solution is also preferably an isotonic solution of saline, but it also contains an enzyme specific for the body analyte of interest. If the body analyte is glucose, then the enzyme is preferably glucose oxidase. The calibration fluid is also preferably an isotonic solution of saline, but it also contains a known concentration of the body analyte of interest. Preferably, the perfusate, enzyme solution, and calibration fluids also contain stabilizers or preservatives as needed to insure that these fluids are stable during their shelf life. Fluid supply lines 31, 32, and 33 are made of any of a number of flexible tubing materials such as Tygon and silicone rubber. Fluid containing reservoirs 20, 21, and 22 are made of any of a number of laminated films composed of a fluid compatible fluid contacting inner layer of, for example, polyethylene, and a gas and vapor impermeable layer such as aluminum. Other layers in the laminate may be, as needed, a material such as PET for tensile strength and a light absorbing layer for radiation protection. Fluid is caused to flow from these reservoirs to the analysis chamber by pumping means 24, 25, and 26 as shown in Figure 1 such as one or more positive displacement pumps, but preferably by pressure applied to the reservoirs by constant pressure springs (not shown—for example, the springs described in Sage, et. al. in US 5,957,895). These three fluids, the perfusate, the enzyme containing fluid, and the calibration solution, are sequenced into microfluidics chip 1 by means of fluid sequencing

subsystem 36, shown in greater detail in Figure 4. All fluids pass through microfluidics chip 1 and are collected in waste container 37.

**Please amend paragraph 0029 as follows:**

In order to collect a sample of the body fluid, microdialysis needle 3 is placed in a body fluid, preferably interstitial fluid just below the surface of skin. As shown in Figure 2, perfusate flows into microdialysis chip 1 through perfusate entry 2, and flows the entire length of microdialysis needle 3 from the end proximal to microdialysis chip 1 to its distal end and back to the proximal end before passing back into microdialysis chip 1 and through check valve 5. As the perfusate passes through microdialysis needle 3, body analyte enters the perfusate by diffusion through a semipermeable membrane 12, shown in greater detail in Figure 3, which shows a cross section of microdialysis needle 3 along line A---A in Figure 2, which represents a cross-section taken on a plane normal to the longitudinal axis of the needle 3. In a preferred embodiment of the invention, the flow rate through microdialysis needle 3 is 1 nanoliter per second, and the dimensions (cross-section) of the lumen 11 of microdialysis needle 3 are 20 microns high by 50 microns wide. The semipermeable region of microdialysis needle 3 is 5 millimeters long, making the region of microdialysis 10 millimeters in length. Of course, another preferred embodiment may utilize needles with different dimensions, such as a microfabricated microdialysis needle 150 microns wide by 100 microns thick, as discussed above. Moreover, another preferred embodiment may utilize a microdialysis needle with a lumen having a cross-sectional area less than 5000 square microns. Moreover, another preferred embodiment may utilize a microdialysis needle with a lumen having a width to height ratio of the cross-sectional area larger than 1.5:1. Of course, another preferred embodiment may utilize different

**ratios, as may be seen from the dimensions detailed above.** Thus the transit time of fluid entering the microdialysis needle 3 is ten seconds. Given the rapid diffusion of low molecular body analytes such as lactate and glucose (the diffusion constant for glucose in a low viscosity fluid such as water is  $6.7 \times 10^{-6} \text{ cm}^2/\text{sec}$ ) and the relatively shallow lumen of microdialysis needle 3, diffusion equilibrium for the analyte is rapidly reached between the interstitial fluid and the perfusate. In the preferred embodiment described here, the equilibrium time is 0.6 seconds (diffusion time is calculated using the equation  $t = x^2/D$  where  $t$  is the diffusion time,  $x$  is the diffusion distance, in this case the height of the lumen of the microdialysis needle, and  $D$  is the diffusion constant). In this preferred embodiment a high yield of the body analyte in the perfusate is provided and reduction of the concentration of the body analyte in the tissue adjacent the microdialysis needle is avoided.

**Please add the following paragraph immediately after paragraph number 0037:**

The system may be configured to reside on the body of a person, as is shown in Figure 5 or Figure 6. Figure 5 shows such a system 52 being held on body part 53 by strap 51. Figure 6 shows system 62 being held on the skin with an adhesive and being used in conjunction with a means for administering insulin 61.